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Neurofibromatosis Type 1 And Its Prenatal Diagnosis.

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ABSTRACT

Neurofibromatosis is the most common of the phakomatoses, with a prevalence of 1in 3,000-4,000.Neurofibromatosis 1(NF1) also known as Von Reclinghausen disease, is an autosomal dominant condition caused by mutation of NF1 gene,which is located at chromosome 17q11.2. NF1 is believed to be completely penetrant,but substantial variability in expression of features occurs.It is a multisystem disorder that primarily involves the skin and nervous system.The condition usually is recognised in early childhood,when café au lait macules are apparent.NF1 is predisposed to CNS tumors including optic glioma,astrocytoma and plexiform neurofibroma.

Keywords: Neurofibromatosis type1, Inheritance, prenatal diagnosis

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INTRODUCTION

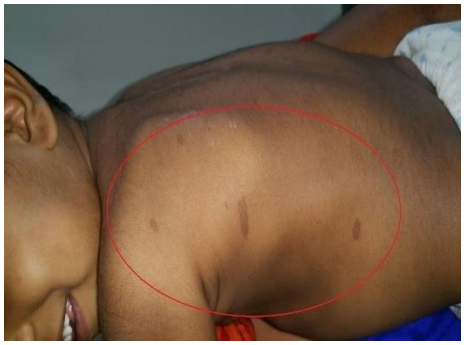
Neurofibromatosis are autosomal dominant disorders that cause tumors to grow on nerves and result in other abnormalities such as skin changes and bone deformities. NF 1 is the most prevalent type with an incidence of 1 in 3000 [1]. NF 2 is a rarer condition with an incidence of 1 in 25,000 [1]. NF 1 is an autosomal dominant disorder. NF1 gene on chromosome region 17q11.2 encodes a protein also known as neurofibromin. Neurofibromin acts as an inhibitor of the oncogene ras[2]. Diagnosis of NF1 is based on clinical features.

The purpose of this case report is to illustrate the clinical criteria, the inheritance pattern of NF1, the prenatal diagnosis and to give some recommendations about genetic councelling as molecular testing is available and can be useful in number of cases.

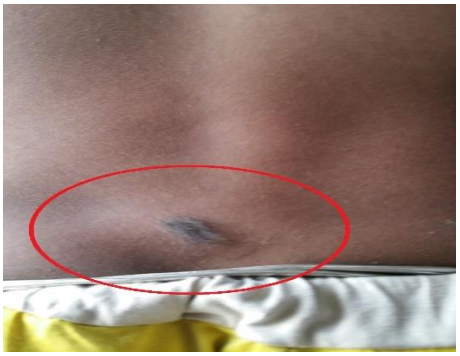
CASE REPORT

A 5 year old male child was brought to our pediatric OPD for evaluation of multiple brownish patches over the trunk and back since birth. His sibling as well as his mother had similar complaints. The child was a first born of a non-consangunious marriage and he was developmentally normal. There was no history of seizures or learning difficulty. On examination the child was active, well-nourished and multiple café au lait spots were noticed over trunk and back as shown in pic-1.In addition a tuft of hair was noticed over the lumbar region in the midline as shown in pic-2.Systemic examination was normal ,fundus was normal - no lisch nodules. MRI brain and spine done suggestive of Bilateral symmetrical T2 and T2 FLAIR hyperintensities in bilateral globus pallidus – consistent with neurofibromatosis (Fig.1)Two thin T2 FLAIR hyperintense subdural collections in the left parietal region and left temporal region- ? Chronic subdural hematoma(Fig.2)Extra axial CSF signal intensity collection in the left anterior temporal fossa with mild mass effect of adjacent temporal lobe- ARACHNOID CYST(Fig.3).Incomplete fusion of laminae with lack of normal spinous process seen at L5 level- spina bifida occulta(Fig.4).

Our provisional diagnosis was Type 1 Neurofibromatosis with Spina bifida occulta.



Pic-1 Café Au Lait Spots



Pic -2 Tuft Of Hairs

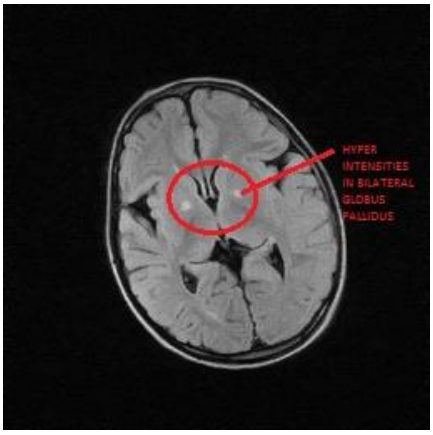


Fig1.Hyperintensities In Globus Pallidus

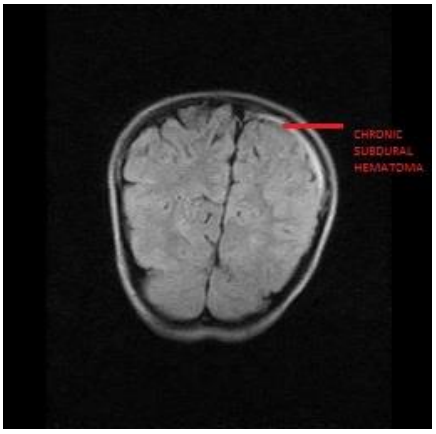


Fig 2.Chronic Subdural Hematoma

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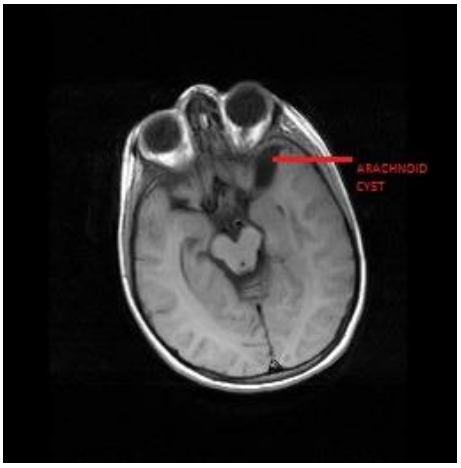

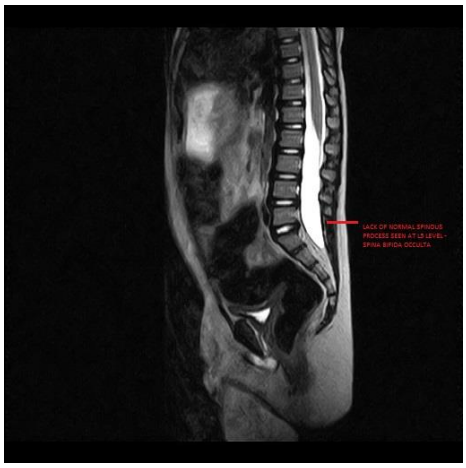

Fig 3. Arachnoid Cyst **Fig 4.Spina Bifida Occulta**

DISCUSSION

NF 1 is diagnosed when any 2 of following 7 features are present [3]

1. Café au lait macules 6 or more over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals. Café au lait are hallmark of NFand spots are scattered over body surface with predilection for trunk and extremities but sparing the face.
2. Axillary or inguinal freckling constituting of multiple hyperpigmented areas of 2-3 mm in diameter which appears between 3-5 years of age
3. Iris lisch nodules 2 or more – these are hamartomas located within the iris and are identified by a slit lamp examination
4. Neurofibromas 2 or more typically involving the skin or one plexiform neurofibroma which is usually evident at birth and result from diffuse thickening of nerve trunks that are frequently located in the orbital or temporal region of face
5. A distinctive osseous lesion such as sphenoid dysplasia or cortical thinning of long bones
6. Optic gliomas – in 15 % of patients with NF1 and represent mostly low grade astrocytomas
7. First degree relative with NF 1

MRI features- Showing abnormal hyperintense T2 weighted signals in the optic tracts, brainstem,globuspallidus, thalamus, internal capsule and cerebellum-UBO(Unidentified bright object).

NF 1 is an autosomal dominant disorder. NF1 gene on chromosome region 17q11.2 encodes a protein also known as neurofibromin. Neurofibromin acts as an inhibitor of the oncogene ras [2]. Diagnosis of NF1 is based on clinical features as described above. However molecular testing for NF1 is available and can be useful in number of cases. Genetic testing is necessary to provide prenatal diagnosis and may be used as an adjunct to clinical diagnosis in cases with an atypical presentation. This involves analysis of both mRNA and genomic DNA, includes real-time polymerase chain reaction, direct sequencing, microsatellite marker analysis, multiplex ligation-dependent probe amplification, and interphase fluorescence in situ hybridization [4]. Testing by fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, or analysis of multiple single nucleotide polymorphisms (SNPs) or other polymorphic genetic markers in the NF1 genomic region is sometimes performed to look just for whole NF1 gene deletions when the “large deletion phenotype” is suspected clinically[4]. Whole NF1 gene deletions occur in 4% to 5% of individuals with NF1.

Prenatal diagnosis of exceptionally severe NF1 can be made by ultrasound. If prenatal diagnosis is suggestive of NF1, parents can be councelled regarding disease related complications and termination of pregnancy [5].

For the patients with NF 1 MRI should be done and they should have regular clinical assessments atleast yearly. These assessments include ophthalmologic examination, neurologic assessment, and blood pressure

monitoring and scoliosis evaluation. Neuropsychologic and educational testing should be considered as needed because they are prone for Learning disability -30%,Seizures-8%,Scoliosis-10%,Malignant neoplasms-3%,Cerebral vessel aneurysm, Transient cerebrovascular ischaemic attacks, Hemiparesis, Cognitive defects, Risk for hypertension resulting from renal vascular stenosis and pheochromocytoma [6].

CONCLUSION

Prenatal diagnosis and genetic testing is important for early diagnosis of Neurofibromatosis 1. Parents can be counselled for regular follow up regarding treatment and other investigation modalities.

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